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(54) Flash-melt oral dosage formulation

(57) There is provided granules for the production of flash-melt pharmaceutical oral dosage forms. In addition to one or more medicaments, the granules are composed of an excipient combination consisting of a superdisintegrant, a dispersing agent, a distributing agent, and a binder and may also include other conventional ingredients such as sweetening and flavoring agents. The subject granules are advantageous in that they are stable and can be prepared without the aid of solvents and without the need for special environments or handling. Dosage forms, especially tablets, prepared therefrom on conventional equipment disintegrate in the mouth in under about twenty five seconds.

EP 1 145 711 A1

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Field of the Invention

[0001] The present invention relates to a formulation for solid pharmaceutical oral dosage forms that disperses in the mouth in under about 25 seconds.

Background of the Invention

[0002] There are a number of varieties of solid pharmaceutical dosage forms that rapidly dissolve or disintegrate in a glass of water, in the mouth, or in the gastrointestinal tract. Such dosage forms have been known in the art for many years. The obvious advantages of the convenience of carrying dosage forms that will dissolve or effervesce in water to release medicaments are well known. Likewise, the therapeutic need of having an oral dosage form that will rapidly dissolve or disintegrate in the mouth for situations where immediate medication is necessary and water is not available has long been recognized.

[0003] Initially, a distinction must be drawn between flash-melt dosage forms and rapidly disintegrating dosage forms. The former are intended to dissolve or disintegrate in the mouth of the patient in less than one minute whereas the latter are intended for primary dissolution or disintegration within 3 to 20 minutes in the acidic medium of the stomach or a container of water. The recognized test for rapidly disintegrating dosage forms is disintegration time in 0.1 N hydrochloric acid. Those of ordinary skill in the art will appreciate that the requirements for formulating dosage forms to meet these criteria must necessarily be different since the conditions, particularly pH, in the mouth and the stomach are quite different. More important, the time in which a dosage form must dissolve or disintegrate in the mouth is necessarily much shorter than in the stomach with the obvious exception of dosage forms, e.g. lozenges, that are specifically formulated to slowly dissolve in the mouth.

[0004] Another consideration common to most if not all dosage form formulations intended for flash-melt or rapid disintegration is the need to take precautions in the preparation, packaging, handling and storing of the finished dosage forms since they tend to be both hygroscopic and friable. Dosage forms dependent on effervescence to promote their disintegration are particularly susceptible to moisture and must be packaged with special wrapping, stoppers, packets of drying agent and the like.

[0005] Regardless of such potential problems, there is still an acute need for dosage forms that can rapidly dissolve or disintegrate for the obvious benefits of having a therapeutic dosage of the medicament contained therein available for absorption in a very short time. In addition to the benefits of rapid availability, flash-melt dosage forms are advantageous for administration of medicaments to patients such as the very young, the elderly, the non-compliant and those with a physical impairment that makes it difficult if not impossible to swallow an intact dosage form. Flash-melt dosage forms are further a convenience for situations where potable water may not be readily available or desirable. Medicaments amendable to such dosage forms would include sedatives, hypnotics, antipsychotics, motion sickness medication, mild stimulants such as caffeine and the like.

[0006] Those of ordinary skill in the art are aware that there are two basic compounding concepts recognized for the preparation of rapidly dissolving/disintegrating dosage forms. The first of these, particularly suited for the preparation of flash-melt dosage forms, is freeze drying wherein a cake or wafer is prepared from a freeze-dried solution or suspension of medicament and suitable excipients in water or other solvents. Such wafers dissolve very rapidly on the tongue, i.e. within about ten seconds, due to a combination of a high affinity for moisture resulting from the freeze drying process and a very high porosity, which promotes rapid ingress of saliva. While such dosage forms are capable of rapid disintegration/dissolution in the mouth, the freeze drying process suffers from several disadvantages, primary among which is the fact that a solution or a stable suspension of the medicament must be formed before it can be freeze dried. While not always the case, typically such solutions are aqueous and, therefore, not suited to formulating medicaments sensitive to water. The process itself is typically laborious and time-consuming. Finally, the resultant dosage forms, in addition to being hygroscopic, tend to be very soft and, therefore, require special moisture-and impact-resistant packaging and require careful handling prior to administration.

[0007] The second major technology utilized in the manufacture of rapidly disintegrating dosage forms is based on special grades of sugars such as mannitol, sorbitol and the like in combination with superdisintegrants. The latter are excipients that are characterized by a special wicking capacity to channel water into the interior of the dosage form, or by rapid swelling in water, both of which act to hasten disintegration. It is also known to enhance dissolution of dosage forms by the inclusion of effervescent combinations, typically sodium bicarbonate and a weak acid, such as citric acid. As noted above, effervescent formulations require special moisture resistant packaging as even very small levels of moisture may be sufficient to initiate the effervescent reaction. Techniques, such as fluidized bed granulation, are recognized as being useful in the preparation of such formulations. Too often, however, such technologies require a specific, very costly plant including special handling equipment, controlled-humidity environments and the like. In

spite of such measures, dosage forms produced by such techniques typically require moisture resistant packaging, the need to include in the packaging packets or capsules of moisture absorbing agents and the like.

[0008] An example of a teaching of the incorporation of super disintegrants in dosage form formulations to enhance dissolution is WO 98/030640, FMC Corporation. It is disclosed therein that, for cost considerations, up to 90% of a group of super disintegrants including cross-linked cellulose, cross-linked carboxymethyl cellulose, cross-linked starch, croscarmellose alkali metal salt, crospovidone, alkali metal starch glycolate and the like can be replaced by a co-disintegrant. Included among the latter group are natural diatomaceous silica, a synthetic hydrous alkaline earth metal calcium silicate and a porous hydrophilic zeolite. The weight ratio of super disintegrant to co-disintegrant is stated as from 4:1 to 1:10, preferably 2-1:1. There is no indication of any recognition of benefits to be derived from the formulation other than the obvious consideration of cost savings since the co-disintegrants are less expensive and the combination is stated to accomplish the desired results.

[0009] In contrast, Japanese patent 10114655, Kyowa Hakko Kogyo KK discloses a formulation intended for rapid dissolution in the stomach that can contain up to 30% by weight of a superdisintegrant, such as crospovidone or hydroxypropylcellulose, croscarmellose and the like and up to 30 % of a neutral or basic ingredient including magnesium aluminum metasilicate, calcium silicate, a phosphoric acid salt or a metal hydroxide. The dosage form is intended for medicaments that produce a gel at acidic pH.

[0010] There are numerous other examples of specific formulations that utilize one or more of the techniques or mechanisms discussed above. For the most part, however, they also possess one or more of the enumerated disadvantages to some degree, e.g. it is difficult or expensive to produce dosage forms by such techniques, the resulting dosage forms are friable or are sensitive to environmental factors such as moisture. There continues to be the need for a formulation that mitigates or eliminates these disadvantages, yet yields a flash-melt dosage form that will disintegrate in the mouth within about 25 seconds. Such formulations are provided in accordance with the present invention.

Summary of the Invention

[0011] A formulation is disclosed which is suitable for the preparation of granules without solvents that can be compressed on conventional equipment into pharmaceutical oral dosage forms, e.g. tablets, caplets, wafers and the like, that will disintegrate in the mouth in under about 25 seconds. The formulation is comprised of a suitable medicament and a four component excipient combination consisting of a superdisintegrant, a dispersing agent, a distributing agent, and binder that also functions as a wicking agent to promote ingress of fluids into the dosage form and may also include other conventional ingredients such as sweetening and flavoring agents. The preparation of the formulation of the invention is unique in that the combination of four excipients can be dry granulated with the medicament and suitable conventional ingredients, such as flavoring and sweetening agents, without the use of any solvent, to form stable granules that can be readily compressed into dosage forms on conventional equipment without the need for special handling techniques. In a particular embodiment, granules are formed containing the medicament and other ingredients and a majority of the excipient combination. The granules are then blended with the remaining ingredients to form a final blend suitable for direct compression into dosage forms on conventional equipment.

[0012] A three component excipient combination comprising of a superdisintegrant, a dispersing agent and a binder is provided as another object of the invention. This dosage form may be a tablet in which, the superdisintegrant is selected from the group consisting of crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose and pregelatinized starch, said dispersing agent is selected from the group consisting of ortho-, meta- and alpha triclinic-calcium silicate, ortho- and meta-magnesium trisilicate and silicic acid, and said binder is selected from the group consisting of microcrystalline cellulose, hydroxypropyl cellulose, ethyl cellulose, lactose, mannitol and calcium phosphate.

Detailed Description of the Invention

[0013] The formulation of the present invention and the process of preparing flash-melt dosage forms therefrom are based on a combination of four excipients. This unique combination of excipients may be formulated with other conventional adjuncts, particularly flavoring agents, sweetening agents, lubricants and the like and one or more active medicaments as will be discussed below. The active medicament may comprise up to about 30% by weight, preferably up to about 15% by weight, of the formulation, depending on the amount required for a therapeutically effective dosage and factors such as its capacity to be directly granulated, the amount of flavoring/sweetening agents required to mask the taste or bitterness thereof and the like. It is within the scope of the present invention to utilize medicaments that are coated for taste or other reason in the subject formulations provided that the coatings do not interfere with either the compounding or the disintegration of the tablets. The excipient combination comprises, in total, up to about 85% by weight, preferably from about 50% to about 80% by weight, of the formulation.

[0014] The excipient component of the formulations of the present invention is a combination of a superdisintegrant,

a dispersing agent, a distributing agent, and a binder. Suitable superdisintegrants include crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropylcellulose, pregelatinized starch and the like. The preferred superdisintegrant for the subject formulations is crospovidone since it can be utilized in large amounts without causing a formulation containing it to have a propensity to gel.

[0015] Suitable dispersing agents, also sometimes referred to in the art as anticaking agents, include calcium silicate-ortho, meta and alpha triclinic forms thereof, magnesium trisilicate-ortho and meta forms thereof and silicic acid. Calcium silicate is the preferred dispersing agent. Particularly preferred is a crystalline alpha triclinic calcium silicate, commercially available from Aldrich Chemical Company which meets the following specifications: 1.3 m^2/gm surface area; 0.63 g/cc bulk density; 2.90 g/cc true density; and < 1% w/w volatiles. A variety of pharmaceutical grades of calcium silicate available from other vendors, as shown in Table 1, have also been found to produce satisfactory flash-melt dosage forms as well. These include ortho and meta forms of calcium silicate available from Alfa-Aesar, synthetic calcium silicates Micro-cel C and Micro-cel E, available from Celite Corp, Hubersorb 600 NF and Hubersorb 250 NF available from J. M. Huber Corp, and combinations of various grades thereof. These products have been found to cover the following range of specifications for calcium silicate: 1.0 m^2/gm to 210 m^2/gm surface area; 0.075 g/cc to 0.90 g/cc bulk density; 1.70 g/cc to 2.90 g/cc true density; and < 1% to 14% w/w volatiles. Table 1 lists the individual specifications for each of the materials obtained from the vendors listed above.

Table 1.

Source	Description	Surface area m^2/gm	Bulk Density g/cc (± s.d.)	True Density g/cc	Volatiles (% w/w)
Aldrich Aldrich	CaSiO3 < 200mesh (crystalline, alpha triclinic)	1.3	0.627 (0.020)	2.934	0.50
Alfa Aesar	2CaO.SiO2 (crystalline, ortho)	0.98	0.492 (0.003)	3.252	0.02
Alfa Aesar	CaSiO3 (crystalline, meta)	2.5	0.867 (0.009)	2.940	0.50
Celcite	Micro-cel E (crystalline)	90.4	0.094 (0.006)	2.596	0.94
Celcite	Micro-cel C (amorphous)	191.3	0.120 (0.006)	2.314	5.11
JM Huber	Hubersorb 250NF (amorphous)	103.0	0.130 (0.008)	1.702	9.90
JM Huber	Hubersorb 600NF (amorphous)	209	0.075 (<0.001)	2.035	13.8

[0016] Alpha triclinic calcium silicate is advantageously combined in the subject formulations with at least one other pharmaceutical grade of calcium silicate wherein the alpha triclinic form would comprise from about 10% to about 90% by weight of the combination. In contrast to its use in conventional tabletting formulations, it is considered unexpected that the dispersing agent, i.e. calcium silicate, is the primary constituent of the excipient combination of the subject formulations since it is generally recognized by those of ordinary skill in the art as being poorly compressible.

[0017] Examples of suitable distributing agents for the excipient combination of the subject formulations include amorphous silica, fumed silica, diatomaceous earth, talc, kaolin, magnesium aluminum trisilicate and the like, with amorphous silica being especially preferred.

[0018] The final component of the excipient combination of the formulations of the invention is a binder. Suitable binders are those that also function as a wicking or distributing agent in that they act to promote water intake into dosage forms made therefrom. Suitable binders include carbohydrates such as, microcrystalline cellulose, hydroxypropyl cellulose, ethyl cellulose, starch, lactose, and also, mannitol and calcium phosphate. Microcrystalline cellulose

is the preferred binder. Microcrystalline cellulose is commercially available as Avicel® PH (pharmaceutical grade) from FMC Corporation, Philadelphia, Pa., particularly Avicel® PH 101, PH 102, PH 103, PH 112, PH 200, PH 301, PH 302 and Ceolus. Microcrystalline cellulose is also available from Mendell, Penwest Company, Patterson, N.Y., as Emcocel ® 90M and Emcocel ® 50M, which could be used satisfactorily. Particularly preferred in the present formulations is Avicel® PH 102 or a combination of Avicel® PH 102 and Avicel® PH 200 as will be described below.

[0019] In a preferred embodiment of the present invention, the excipient combination of the present formulations comprises crospovidone as the superdisintegrant, calcium silicate as the dispersing agent, amorphous silica as the distributing agent and microcrystalline cellulose as the binder. The range of the members of the excipient combination of the subject formulations is from about 4 to about 8, preferably from about 5 to about 7, percent by weight of the superdisintegrant; from about 20 to about 70, preferably from about 35 to about 45, percent by weight of the dispersing agent; from about 1 to about 10, preferably from about 1.5 to about 3, percent by weight of the distributing agent; and from about 10 to about 50, preferably from about 12 to about 20, percent by weight of the binder, all based on the overall weight of the formulation including one or more medicaments. A particularly preferred excipient combination comprises about 7 percent by weight of the superdisintegrant, about 40 percent by weight of the dispersing agent, about 2 percent by weight of the distributing agent and about 15 percent by weight of the binder, based on the total weight of the formulation including medicament(s).

[0020] The formulations of the present invention may contain other conventional ingredients found in similar preparations known in the art and recognized as approved for use in preparations to be taken into the body. These would include, for example, natural and artificial flavors, polyols such as mannitol, sorbitol, maltitol and xylitol, artificial sweetening agents such as, N-α-L-Aspartyl-L-phenylalanine 1- methyl ester (aspartame) and 6-methyl-3,4-dihydro-1,2,3-oxathiazin-4(3H)-one-2,2-dioxide, particularly the potassium salt thereof (acesulfame K), flavor adjuncts such as tartaric acid, tabletting lubricants, such as magnesium stearate, and the like. Those skilled in the art of pharmaceutical compounding will appreciate that the amount of flavoring and sweetening agents, if any, present in the formulations of the present invention will be directly proportional to the taste or bitterness of the medicament. The flavoring and sweetening agents do not serve to coat the medicament, but are adequate to mask the objectionable taste of the medicaments in homogeneous admixture therewith. In general, the total of such conventional ingredients will not exceed about 32 percent, preferably from about 25 to about 30 percent by weight based on the total weight of the formulation.

[0021] The medicament in the formulations of the present invention typically will not exceed about 30 percent by weight, preferably from about 1 to about 15 percent by weight of the formulation. Those of ordinary skill in the art will appreciate that the physical characteristics of the medicament itself, i.e. its particle size and morphology, will directly influence its limiting content in the subject formulations. Clearly, there has to be sufficient medicament in the dosage form produced form the subject formulations to provide a therapeutically effective dosage. While solid dosage forms can be prepared from the formulations of the present invention by any recognized technique, including wet granulation, it is a particular advantage that the formulations can be dry granulated without the use of specialized equipment and conditions, thereby making them suitable for the formulation of medicaments that are sensitive to moisture and high temperatures.

[0022] Examples of medicaments that can be formulated into flash-melt tablets in accordance with the present invention include, without intended limitation, antihistamines, anti-motion sickness agents, analgesics, antiinflammatory agents, antibiotics, cholesterol lowering agents, anti-anxiety agents, anti-hypertensives, anti-cancer agents, hypnotics, anti-ulcer agents, coronary dilators, antivirals, anti-psychotics, anti-depressants, neuromuscular agents, anti-diarrheals, hypoglycemic agents, thyroid suppressors, anabolic agents, antisposmodics, antimigraine agents, diuretics, stimulants, decongestants, uterine relaxants, anti-arrhythmics, male erectile dysfunction compounds, Maxi-K channel openers or neuroprotective agents for the treatment of stroke or Alzheimer's disease and therapeutically appropriate combinations thereof. Specific therapeutic agents falling into the foregoing categories include, again without intended limitation, aripiprazole, ibuprofen, aspirin, acetaminophen, chlorpheniramine maleate, psuedoephedrine, diphenhydramine HCl, ranitidine, phenylpropanolamine, cimetidine, loperamide, meclizine, caffeine, entecavir, cefprozil, melatonergic agonists, pravastatin, captopril, fosinopril, irbesartan, omapatrilat, gatifloxacin and desquinolone and therapeutically appropriate combinations thereof.

[0023] As stated above, a decided advantage of the formulation of the present invention is that it can be dry-granulated into stable, fine granules that can be directly compressed into pharmaceutically elegant flash-melt oral dosage forms, e.g. tablets, caplets, wafers and the like. Preferably, the granules for flash-melt dosage forms in accordance with the present invention are formed in two steps. The process comprises initially forming granules, referred to herein as the intragranulation, by blending all of the medicament, the dispersing agent, distributing agent, other conventional ingredients as described above and a portion of each of the superdisintegrant, binder and tabletting lubricant together in a suitable mixer to assure uniform distribution throughout. A conventional V-blender is a preferred apparatus for this step. While a minor portion of the dispersing agent may be omitted from the intragranulation, it is preferred that all be incorporated therein. The blended mixture is then compacted in a conventional roller compactor having an orifice such that the compacts thereof are in the form of ribbons. Alternately, a slugging process can be used. The compacts from

the roller compactor or the slugs from the slugger are passed through a fine screen, e.g. a 30 mesh (600 microns) screen, thereby breaking them into granules between about 150 and 400 microns in size. The intragranulation granules thus-prepared are thereafter blended in a suitable mixer with the remaining ingredients, i.e., superdisintegrant, binder and lubricant, referred to herein as the extragranulation ingredients, to form a final blend that can be directly compressed into pharmaceutical dosage forms utilizing conventional equipment such as a tablet press. Rather than directly compress the final blend upon formation, since it is stable, it can be stored and subsequently pressed into dosage forms at a later time. It is a decided advantage of the subject invention that these operations are carried out without the need to resort to special handling such as taking precautions against any moisture coming in contact with the ingredients or the granules, and without the use of specially controlled temperature and humidity conditions.

[0024] The intragranulation comprises from about 80 to 99, preferably from about 85 to 95, most preferably about 90, percent by weight of the final blend. Based on the weight of the final blend, the intragranulation preferably comprises up to about 30 percent by weight, preferably from about 6 to 20 percent by weight, of the binder, up to about 5 percent by weight, preferably from about 2 to 4 percent by weight, of the superdisintegrant, and all of the dispersing agent and the distributing agent. The binder and superdisintegrant are divided between the intragranulation and the extragranulation ingredients in weight ratios of approximately 2:1 to 4:1 for the binder and 0.5:2.0 to 2.0:0.5 for the superdisintegrant. The conventional tabletting lubricant is divided approximately equally between the intragranulation and the extragranulation ingredients.

[0025] The final blend is formed by mixing the intragranulation and the extragranulation components of the excipient combination, adding the remaining tabletting lubricant thereto and blending until uniform. Alternatively, a direct compression approach can be utilized in which all of the ingredients with the exception of the tabletting lubricant are mixed in a suitable blender, such as a conventional V-blender, by geometrically building the entire mass of the formulation via sequential blending for three minutes after each addition, and finally adding the lubricant to the mixture after all other ingredients have been blended.

[0026] Tablets compressed on a conventional tablet press from the final blend obtained from either a one-step granulation or a direct compression blend, were pharmaceutically elegant and disintegrated in water within ten seconds. A tablet is considered as disintegrated when it has totally broken down to granules and there are no discernible lumps remaining. Since the medicament is not intimately bound to any of the ingredients of the formulation, it is released within the same time period. The most outstanding advantage of the subject formulations is that dosage forms can be manufactured therefrom which are robust and, hence, avoid the need for specialized unit dose packaging and careful handling during manufacture or use as is often the case with present dosage forms. The dosage forms prepared from the formulations of the present invention can be packaged in conventional blister packs or in HDPE bottles.

[0027] It is understood that various other embodiments and modifications in the practice of the invention will be apparent to, and can be readily made by, those of ordinary skill in the art without departing form the scope and spirit of the invention as described above. Accordingly, it is not intended that the scope of the claims appended hereto be limited to the exact description set forth above, but rather that the claims be construed as encompassing all of the features of patentable novelty that reside in the present invention, including all the features and embodiments that would be treated as equivalents thereof by those skilled in the art to which the invention pertains. The invention is further described with reference to the following experimental work.

EXAMPLE 1

[0028] Flash-melt tablets were prepared as follows:

Intragranulation:		
Ingredient	Percent w/w	Mg. per tablet
Xylitol (300) Xylisorb	26	52
Avicel® PH 102	12	24
Calcium Silicate	43.35	86.7
Crospovidone	3	6
Amorphous silica	2	4
Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4

(continued)

Intragranulation:		
Ingredient	Percent w/w	Mg. per tablet
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	92.75	185.5

[0029] The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was then added and the mixture blended for an additional three minutes. The blended formulation was compacted at a pressure of 30-35 kgF/cm^2 in a commercial compactor equipped with an orifice such that the compacts therefrom are in the form of ribbons. The ribbons were passed through a 30 mesh (600 microns) screen to form stable granules of about 150 to 400 microns.

Extragranulation Ingredients:		
Ingredient	Percent w/w	Mg. per tablet
Intragranulation	92.75	185.5
Avicel® PH 200	3	6
Crospovidone	4	8
Magnesium stearate	0.25	0.5
Total weight	100	200

[0030] The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 2.3 kP (3.5 SCU) and disintegrated in 10 seconds in 5 ml of water. The final blend formulation demonstrated excellent flow and was free of other problems such as chipping, capping and sticking. It has been found that utilizing Avicel® PH 102 for the intragranulation and Avicel® PH 200 for the extragranulation ingredient enhanced the quality of the resultant tablets.

EXAMPLE 2

[0031] Flash-melt tablets containing a combination of two grades of calcium silicate were prepared as follows:

Intragranulation:		
Ingredient	Percent w/w	Mg. per tablet
Xylitol (300) Xylisorb	26	52
Avicel® PH 102	12	24
Calcium Silicate (crystalline, alpha triclinic)	33.35	66.7
Hubersorb 600 NF (amorphous calcium silicate)	10	20
Crospovidone	3	6
Amorphous silica	2	4
Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	92.75	185.5

[0032] The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was added and the mixture blended for an additional three minutes. The blended formulation was compacted, and screened to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:		
Ingredient	Percent w/w	Mg. per tablet
Intragranulation	92.75	185.5
Avicel® PH 200	3	6
Crospovidone	4	8
Magnesium stearate	0.25	0.5
Total weight	100	200

[0033] The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 2.0 kP (3.1 SCU) and disintegrated in 10 seconds in 5 ml of water.

EXAMPLE 3

[0034] Flash-melt tablets containing aripiprazole, an antischizophrenic drug, were prepared as follows:

Intragranulation		
Ingredient	Percent w/w	Mg. per tablet
Aripiprazole	15	30
Xylitol (300) Xylisorb	25	50
Avicel® PH 102	6	12
Calcium Silicate	37	74
Crospovidone	3	6
Amorphous silica	2	4
Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	94.4	188.8

[0035] The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was added and the mixture blended for an additional three minutes. The blended formulation was compacted, and screened to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:		
Ingredient	Percent w/w	Mg. per tablet
Intragranulation	94.4	188.8
Avicel® PH 200	1.1	2.2

(continued)

Extragranulation Ingredients:		
Ingredient	Percent w/w	Mg. per tablet
Crospovidone	4	8
Magnesium stearate	0.5	1
Total weight	100	200

[0036] The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 2.0 kP (3.1 SCU) and disintegrated in 10 seconds in 5 ml of water.

EXAMPLE 4

[0037] Flash-melt tablets containing aripiprazole were prepared as follows:

Intragranulation:		
Ingredient	Percent w/w	Mg. per tablet
Aripiprazole	0.5	1
Xylitol (300) Xylisorb	27	54
Avicel® PH 102	12	24
Calcium Silicate	42	84
Crospovidone	3	6
Amorphous silica	2	4
Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	92.9	185.8

[0038] The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was added and the mixture blended for an additional three minutes. The blended formulation was compacted, and screened to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:		
Ingredient	Percent w/w	Mg. per tablet
Intragranulation	92.9	185.8
Avicel® PH 200	2.6	5.2
Crospovidone	4	8
Magnesium stearate	0.5	1
Total weight	100	200

[0039] The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three

minutes to form the final blend. Tablets compressed therefrom had a breaking force of 2.3 kP (3.5 SCU) and disintegrated in 10 seconds in 5 ml of water.

EXAMPLE 5

[0040] Flash-melt tablets can be prepared containing the antiviral medicament entecavir as follows:

Intragranulation:		
Ingredient	Percent w/w	Mg. per tablet
Entecavir	1	2
Xylitol (300) Xylisorb	26	52
Avicel® PH 102	10	20
Calcium Silicate	45	90
Crospovidone	4	8
Amorphous silica	2.	4
Aspartame	2	4
Wild cherry flavor	0.25	0.5
Tartaric acid	2	4
Acesulfame K	2.	4
Magnesium stearate	0.25	0.5
Total weight	94.5	189

[0041] The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was added and the mixture blended for an additional three minutes. The blended formulation was compacted, and screened to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:		
Ingredient	Percent w/w	Mg. per tablet
Intragranulation	94.5	189
Avicel® PH 200	2	4
Crospovidone	3	6
Magnesium stearate	0.5	1
Total weight	100	200

[0042] The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 2.3 kP (3.5 SCU) and disintegrated in 10 seconds in 5 ml of water. The percent w/w/ ratios taught in this example can also be used to formulate a suitable formulation of the present invention comprising 0.1 mg of entecavir per unit dose.

EXAMPLE 6

[0043] Flash-melt tablets can be prepared containing the antibiotic medicament cefprozil as follows:

Intragranulation:		
Ingredient	Percent w/w	Mg. per tablet
Cefzil	25	125
Xylitol (300) Xylisorb	17	85
Avicel® PH 102	6	30
Calcium Silicate	35	175
Crospovidone	3	15
Amorphous silica	2.	10
Aspartame	2	10
Wild cherry flavor	0.25	1.25
Tartaric acid	2	10
Acesulfame K	2	10
Magnesium stearate	0.25	1.25
Total weight	94.5	472.5

[0044] Blend the ingredients except for the magnesium stearate in a commercial V-blender in geometric proportions for 5 minutes each until all are added. Then add the magnesium stearate to the mixture prepared and mix for an additional three minutes. Then compact the blended formulation, and screen to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:		
Ingredient	Percent w/w	Mg. per tablet
Intragranulation	94.5	472.5
Avicel® PH 200	2	10
Crospovidone	3	15
Magnesium stearate	0.5	2.5
Total weight	100	500

[0045] Place the intragranulation in the blender and add the Avicel® PH 200 and crospovidone thereto and blend for five minutes. Then add magnesium stearate to the mixture and blend for an additional three minutes to form the final blend. Compress tablets therefrom to have a breaking force of 2.5 kP (3.8 SCU) and a disintegration time of 10 seconds or less in 5 ml of water.

EXAMPLE 7

[0046] Flash-melt tablets can be prepared containing the antihypertensive medicament irbesartan as follows:

Intragranulation:		
Ingredient	Percent w/w	Mg. per tablet
Irbesartan	25	125
Xylitol (300) Xylisorb	17	85
Avicel® PH 102	6.	30
Calcium Silicate	35	175
Crospovidone	3	15

(continued)

Intragranulation:		
Ingredient	Percent w/w	Mg. per tablet
Amorphous silica	2	10
Aspartame	2	10
Wild cherry flavor	0.25	1.25
Tartaric acid	2	10
Acesulfame K	2	10
Magnesium stearate	0.25	1.25
Total weight	94.5	472.5

[0047] Blend the ingredients except for the magnesium stearate in a commercial V-blender in geometric proportions for 5 minutes each until all are added. Then add the magnesium stearate to the mixture prepared and mix for an additional three minutes. Then compact the blended formulation, and screen to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:		
Ingredient	Percent w/w	Mg. per tablet
Intragranulation	94.5	472.5
Avicel® PH 20	2	10
Crospovidone	3	15
Magnesium stearate	0.5	2.5
Total weight	100	500

[0048] Place the intragranulation in the blender and add the Avicel® PH 200 and crospovidone thereto and blend for five minutes. Then add magnesium stearate to the mixture and blend for an additional three minutes to form the final blend. Compress tablets therefrom to have a breaking force of 2.5 kP (3.8 SCU) and a disintegration time of 10 seconds or less in 5 ml of water.

Example 8

[0049] Flash-melt tablets can be prepared containing the quinolone antibiotic, des-Quinolone as follows:

Ingredient	Percent w/w	Mg. per tablet
des-Quinolone	20.0	100
Xylitol (300) Xylisorb	22.0	110
Avicel® PH 102	6.0	30
Calcium Silicate	35.0	175
Crospovidone	3.0	15
Amorphous silica	2.0	10
Aspartame	2.0	10
Wild cherry flavor	0.25	1.25
Tartaric acid	2.0	10
Acesulfame K	2.0	10

(continued)

Ingredient	Percent w/w	Mg. per tablet
Magnesium starate	0.25	1.25
Total weight	94.5	472.5

[0050] Blend the ingredients except for the magnesium stearate in a commercial V-blender in geometric proportions for 5 minutes each until all are added. Then add the magnesium stearate to the mixture prepared and mix for an additional three minutes. Then compact the blended formulation, and screen to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:		
Ingredient	Percent w/w	Mg. per tablet
Intragranulation	94.5	472.5
Avicel® PH 200	2.0	10.0
Crospovidone	3.0	15.0
Magnesium stearate	0.5	2.5
Total weight	100	500

[0051] Place the intragranulation in the blender and add the Avicel® PH 200 and crospovidone thereto and blend for five minutes. Then add magnesium stearate to the mixture and blend for an additional three minutes to form the final blend. Compress tablets therefrom to have a breaking force of 2.5 kP (3.8 SCU) and a disintegration time of 10 seconds or less in 5 ml of water.

Example 9

[0052] Flash-melt tablets can be prepared containing the antibiotic gatifloxacin (Tequin®), as a taste masked co-precipitate (30% w/w active) to deliver 50 mg dose:

Intragranulation:		
Ingredient	Percent w/w	Mg. per tablet
Gatifloxacin:stearic acid co-precipitate	33.3	166.7
Xylitol (300) Xylisorb	11.7	58.5
Avicel® PH 102	6.0	30
Calcium Silicate	32.0	160
Crospovidone	3.0	15
Amorphous silica	2.0	10
Aspartame	2.0	10
Wild cherry flavor	0.25	1.23
Tartaric acid	2.0	10
Acesulfame K	2.0	10
Magnesium stearate	0.25	1.25
Total weight	94.5	472.5

[0053] Blend the ingredients except for the magnesium stearate in a commercial V-blender in geometric proportions for 5 minutes each until all are added. Then add the magnesium stearate to the mixture prepared and mix for an additional three minutes. Then compact the blended formulation, and screen to form stable granules in accordance

with the procedure of Example 1.

Extragranulation Ingredients:		
Ingredient	Percent w/w	Mg. per tablet
Intragranulation	94.5	472.5
Avicel® PH 200	2.0	10.0
Crospovidone	3.0	15.0
Magnesium stearate	0.5	2.5
Total weight	100	500

[0054] Place the intragranulation in the blender and add the Avicel® PH 200 and crospovidone thereto and blend for five minutes. Then add magnesium stearate to the mixture and blend for an additional three minutes to form the final blend. Compress tablets therefrom to have a breaking force of 2.5 kP (3.8 SCU) and a disintegration time of 10 seconds or less in 5 ml of water.

Claims

1. A flash-melt pharmaceutical dosage form comprising a medicament and a combination of four excipients consisting of a superdisintegrant, a dispersing agent, a distributing agent, and a binder.

2. A flash-melt dosage form in accordance with Claim 1, comprising not more than about 30 percent by weight of the medicament, and not more than about 85 percent by weight of the total of the combination of four excipients.

3. A flash-melt dosage form in accordance with Claim 2, wherein said combination of four excipients comprises, based on the total weight of the dosage form, from about 4 to about 8 percent by weight of said superdisintegrant, from about 20 to about 70 percent by weight of said dispersing agent, from about 1 to about 10 percent by weight of said distributing agent and from about 10 to about 50 percent by weight of said binder.

4. A flash-melt dosage form in accordance with Claim 3, wherein said combination of four excipients comprises, based on the total weight of the dosage form, from about 5 to about 7 percent by weight of said superdisintegrant, from about 35 to about 45 percent by weight of said dispersing agent, from about 1.5 to about 3 percent by weight of said distributing agent and from about 12 to about 20 percent by weight of said binder.

5. A flash-melt dosage form in accordance with any one of the preceding claims, where said dosage form is a tablet, the superdisintegrant is selected from the group consisting of crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose and pregelatinized starch, said dispersing agent is selected from the group consisting of ortho-, meta- and alpha triclinic-calcium silicate, ortho- and meta-magnesium trisilicate and silicic acid, said distributing agent is selected from the group consisting of amorphous silica, fumed silica, diatomaceous earth, talc, kaolin and magnesium aluminum trisilicate, and said binder is selected from the group consisting of microcrystalline cellulose, hydroxypropyl cellulose, ethyl cellulose, lactose, mannitol and calcium phosphate.

6. A flash-melt tablet in accordance with Claim 5, wherein said superdisintegrant is crospovidone, said dispersing agent is alpha triclinic-calcium silicate, said distributing agent is amorphous silica, and said binder is microcrystalline cellulose.

7. A flash-melt tablet in accordance with Claim 6, wherein said dispersing agent is a combination of alpha triclinic calcium silicate and at least one other pharmaceutical grade of calcium silicate.

8. A flash-melt tablet in accordance with Claim 7, wherein alpha triclinic calcium silicate comprises from about 10% to 90% by weight of the combination.

9. A method of forming granules suitable for compressing into flash-melt dosage forms comprising dry blending into a mixture a medicament, and a combination of four excipients consisting of a superdisintegrant, a dispersing agent, a distributing agent and a binder, compressing the mixture through a suitable compactor or slugger to form com-

pacts or slugs and passing the compacts or slugs through a screen to form granules.

10. A method of forming granules in accordance with Claim 9, wherein said superdisintegrant is selected from the group consisting of crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose and pregelatinized starch, said dispersing agent is selected from the group consisting of ortho-, meta- and alpha triclinic-calcium silicate, ortho- and meta-magnesium trisilicate and silicic acid, said distributing agent is selected from the group consisting of amorphous silica, fumed silica, diatomaceous earth, talc, kaolin and magnesium aluminum trisilicate, and said binder is selected from the group consisting of microcrystalline cellulose, hydroxypropyl cellulose, ethyl cellulose, lactose, mannitol and calcium phosphate.

11. A method of forming granules in accordance with Claim 10, wherein said superdisintegrant is crospovidone, said dispersing agent is alpha triclinic-calcium silicate, said distributing agent is amorphous silica, and said binder is microcrystalline cellulose.

12. A method of forming granules in accordance with Claim 11, wherein said dispersing agent is a combination of alpha triclinic calcium silicate and at least one other pharmaceutical grade of calcium silicate.

13. A method of forming granules in accordance with Claim 9 additionally comprising the step of blending said granules with additional quantities of said superdisintegrant and binder to form a final blend suitable for direct compression into said tablets.

14. A method in accordance with Claim 13, wherein said granules comprise from about 80% to about 99% by weight of said final blend.

15. A flash-melt dosage form formed by compressing the granules of Claim 9.

16. A flash-melt dosage form formed by compressing the granules of Claim 10.

17. A flash-melt dosage form formed by compressing the granules of Claim 13.

18. A flash-melt dosage form in accordance with Claim 17, wherein said dosage form is a tablet and said medicament is entecavir.

19. A flash-melt dosage form in accordance with Claim 17, wherein said dosage form is a tablet and said medicament is cefprozil.

20. A flash-melt dosage form in accordance with Claim 17, wherein said dosage form is a tablet and said medicament is irbesartan.

21. A flash-melt dosage form in accordance with Claim 17, wherein said dosage form is a tablet and said medicament is aripiprazole.

22. A flash-melt pharmaceutical dosage form in accordance with Claim 1 prepared by dry blending into a mixture, a medicament and a combination of four excipients consisting of a superdisintegrant, a dispersing agent, a distributing agent and a binder, compressing the mixture through a suitable compactor or slugger to form compacts or slugs and passing the compacts or slugs through a screen to form granules.

23. A flash-melt pharmaceutical dosage form comprising a medicament and a combination of three excipients consisting of a superdisintegrant, a dispersing agent, a distributing agent, and a binder wherein said superdisintegrant is selected from the group consisting of crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose and pregelatinized starch, said dispersing agent is selected from the group consisting of ortho-, meta- and alpha triclinic-calcium silicate, ortho- and meta-magnesium trisilicate and silicic acid, and said binder is selected from the group consisting of microcrystalline cellulose, hydroxypropyl cellulose, ethyl cellulose, lactose, mannitol and calcium phosphate.

24. A flash-melt dosage form in accordance with Claim 17, wherein said dosage form is a tablet and said medicament is selected from the group consisting of aripiprazole aripiprazole, chlorpheniramine maleate, psuedoephedrine, diphenhydramine HCl, phenylpropanolamine, cimetidine, loperamide, meclizine, entecavir, cefprozil, pravastatin,

captopril, fosinopril, irbesartan, omapatrilat, gatifloxacin and desquinolone.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 00 11 3571

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Place of search	Date of completion of the search	Examiner
THE HAGUE	20 July 2001	Marttin, E

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